Diabetic Complications Consortium

Application Title: Predicting gene expression from pathology images in diabetic kidney disease

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- **Project Accomplishments:**

Project summary: Diabetic kidney disease (DKD) is currently staged by clinical manifestations such as microalbuminuria, overt proteinuria and chronic kidney disease (CKD) and end-stage kidney disease (ESKD). This conventional understanding is questioned by the striking heterogeneity in DKD. In some cases, DKD progresses rapidly towards ESKD and in others, the renal function remains stable despite suboptimal diabetic control. This complex landscape of DKD challenges the current paradigm of grouping patients based on albuminuria or eGFR and begs the question to better characterize the patients with DKD based on the pathway alterations within their kidneys. Although recent explosion in genetic approaches have generated a wealth of information regarding pathway alterations in the single cells of kidneys, there is little translation of such findings to the clinic for direct management of DKD patients. We propose to develop a deep learning framework to associate histomorphologic images with deep -omics data from the same subject to further gain insight on the relationship between gene pathway derived alterations and the histologic features of DKD. Our hypothesis is grounded by the connection between dynamic genomic alterations and tissue-level changes, and we contend that our framework will reveal novel histologically informed molecular targets associated with early and late changes in DKD severity. Using the publicly available -omics and whole slide imaging data from the Kidney Precision Medicine Project, we will build a deep neural network that can predict fold-changes in pathway alterations in specific cell types within the kidney (Aim 1). We will then build another deep neural network that can associate whole slide image-level features with clinical manifestations in DKD patients (Aim 2). Successful completion of this project will develop a computational framework that will predict pathway alterations from the histopathological features from kidney biopsies of DKD patients. Such information will allow clinical translation of genetic information to improve precision in the management of DKD patients. An interdisciplinary team of investigators with a track record of collaboration will pursue these tasks and establish a proof-of-principle phenotype-genotype framework for DKD, which can allow us to apply for future NIH funding.

- **Specific Aims:**

  Aim I: Predict DKD pathway-specific fold changes in gene expression on WSIs. Using the WSI and transcriptomic data from KPMP participants with DKD and controls (without DKD or proteinuria), we will develop a deep neural network that can predict fold-changes in pathway alterations in specific cell-types within the kidney. We will also identify image features that are highly associated with the pathway alterations. The deliverable is a computational framework to identify pathway alterations in specific kidney cell types directly from the morphological features from WSIs of patients with DKD.

Aim II: Associate WSI features with functional alterations in DKD patients. We will develop another deep learning model that can directly associate pathway alterations in specific cell-types with dichotomous clinical outcomes of microalbuminuria and overt proteinuria (presence or absence). The deliverables include a deep neural network that can predict functional outcomes.

Progress: Patients with diabetic nephropathy (DN) often have glomerular, tubular, interstitial, and vascular lesions on biopsy, though a recently proposed DN classification focuses on glomerular features. While it is important to quantify the extent of these histopathological manifestations across all stages of DN, we sought to investigate whether these findings can be identified in early DN patients. During the funding cycle, we developed a deep learning framework known as a feature pyramid network (FPN) to classify digitized renal biopsies as class I or II diabetic nephropathy (DN). PAS-stained whole slide images (WSIs) of cases with class I (n=23) or class II (n=77) DN were divided into training, validation, and test sets in 3:1:1 ratio. This process was repeated five times to achieve a 5-fold cross validation. The FPN expected two inputs, 224x224-pixel patches cropped from WSIs and 16x downsampled WSIs, to learn and combine features at two levels of magnification. Class activation maps (CAMs) were generated to visualize informative regions on the WSIs. Our FPN model achieved an accuracy of 0.8 and an F1 score of 0.6. On a representative set of test images, we found the majority (~84%) of patches identified by CAMs as highly informative for model prediction contained tubules or interstitium, not just glomerular regions (Fig. 1). Our study identified several regions on the biopsy images as informative for prediction of class I vs II DN. Further analysis can elucidate the importance of various histopathological features of early-stage DN. We are currently working to expand this analysis to focus on all the histopathologic stages of DN, followed by analysis of gene expression on these samples.

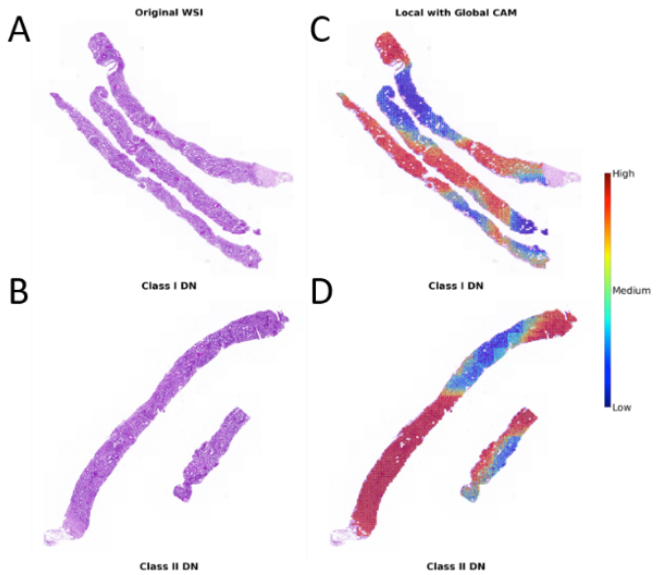

Fig 1: (A and B) Whole slide images and their class labels (Class I & II DN). (C and D) Class activation maps generated on the images, indicating the regions highly associated with the corresponding label. The warmer the color, the higher the probability of a region contributing to the DN class prediction.

- **Publications:**
  - An abstract related to this work was accepted for presentation at the 2022 ASN meeting.
    - 3768041 "Computational assessment of early diabetic nephropathy"
    - Poster Session
      Session Title: Pathology and Lab Medicine [PO1700]
      Session Date, Time: November 3, 2022 from 10:00 AM to 12:00 PM
  - We are also working on a technical manuscript that we plan to submit to a journal for publication in late 2022.